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WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
500 W. MADISON STREET
SUITE 3800
CHICAGO, IL 60661

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,553	YABUBAYASHI ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7,11-14,23-25,28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7,11-14,23-25,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 5/19/2009.

This action examines the claims and arguments presented on 9/24/2008.

Claim status

Claims 1-4, 8-10, 15-22 and 26-27 are canceled..

The amendment has amended claims 24 and 25 from which all pending claims depend.

The amendment has presented new claims 28 and 29.

Claims 5-7, 11-14, 23-25 and 28-29 are pending.

The submission of 5/19/2009 has brought the application into sequence compliance thus the objection to drawings and sequence compliance have been withdrawn.

The objection to claims 26 and 27 has been withdrawn as they are no longer pending.

The 103 rejection based on the combination of Gold and Blackburn has been withdrawn as Gold or Blackburn do not teach or suggest the use of a semiconductor or ceramic fine particle prior to hybridization.

Claim Rejections - 35 USC § 103-New Ground of rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 5, 6, 24-25, and 28 rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (US Patent 5,925, 517 Issued July 20, 1999) in view of Weiss et al (US Patent 5,990, 479 issued (Nov 23, 1999) and Gold et al (WO/1999/31275, Published June 24, 1999) .

Tyagi et al teaches methods of detecting nucleic acids by the use of stem loop structures by the use of interacting labels in which the hybridization of the target sequence to the probe allows for detection (abstract and figure 4). Tyagi teaches, "Any label pair can be used to generate a signal where one member of the pair can detectably alter at least one physically measurable characteristic of the other when in close proximity, but to a different extent when apart. Alternatively, both members may detectably alter such a characteristic of one member when in close proximity, but differently when apart. Additionally, it is necessary that the label moieties must be conjugatable to the probe" (column 16, lines 15-22). Tyagi thus teaches any label pair may be used.

Tyagi further discloses, "Certain embodiments of assays according to the present invention utilize multiple hybridization probes with interactive labels linked to a solid surface or surfaces. Because probes of this invention are used, washing is not required. When probes are linked to a solid surface, we refer to them as "tethered probes." Tethered probes according to this invention must have interactive labels. They may, but need not be, allele-discriminating probes as well. A probe of this type is depicted in FIG. 10, which shows a probe 101 having a target complement sequence 104, complementary arms 105 and 106, and label pair 107, 108 conjugated to arms 105, 106. Probe 101 is tethered to

solid surface 103 by a linking moiety 102. Linking moiety 102 may be covalent or noncovalent. We prefer covalent linkage. Any type of surface 103 may be used, including beads, membranes, microtiter wells, and dipsticks. We prefer surfaces that are neutral with respect to the components of the probe, that is, surfaces that do not interact with nucleic acids, do not interact with the label moieties and do not interfere with the probe signal. An example of such a surface is a surface coated with a siliconizing agent" (column 23, lines 45-65).

Tyagi teaches that the probe can be labeled during synthesis (example I).

Tyagi thus teaches a method of detecting a biochemical reactant by hybridizing a biochemical specimen with a loop-structured nucleic acid probe on a biochip, wherein the free end of loop structured nucleic acid probe is not fixed to the surface of the substrate and detecting is based on optical changes.

Tyagi does not teach the probes are on one or more electrodes on the substrate (claim 24 (a). Tyagi does not teach a first label is either a ceramic fine particle or a semiconductor (claim 24 (b)). Tyagi does not teach wherein attaching the first label takes place in two or more stages.

However, Weiss et al teaches that semiconductor nanocrystals probes are an improvement over other labels as they have a wide absorption band and a narrow emission band, while being stable (column 2, lines 3-15). Weiss teaches that semiconductor nanocrystals can label nucleic acids (column 6, lines 63-66). Weiss teaches that the nanocrystal can be linked to avidin or streptavidin which can target biotin on the probe

(column 10). Thus the use of biotin and avidin or streptavidin results in a two step process of labeling.

Gold et al teach teaches the use of mutually complementary nucleic acids for detection of binding of a target molecule to a nucleic acid ligand (see page 20, lines 26-30). Gold teaches the detection of ligand binding by electronic means (see abstract) and further teaches the use of gold or silver as the substrate for the array (see page 12, line 30). Thus the gold or silver of Gold allow for detection by the transfer of electrons and thus are electrodes (see page 26, lines 7-31).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the semiconductor nanocrystal probes taught by Weiss and the substrate of Gold in the method of Tyagi. The artisan would be motivated because to use the semiconductor nanocrystal labels of Weiss because Weiss teaches the semiconductor nanocrystals are more stable, have a broader absorption spectrum and narrower emission spectrum, further Tyagi suggests any interactive labels can be used. The artisan would have been motivated to use the substrate of Gold in the method of Tyagi because Tyagi teaches any substrate will work and Gold demonstrates that electrodes were a known substrate for loop structure microarrays. It would have further been prima facie obvious to one of skill in the art to compare the optical properties (fluorescence) of the arrays before and after hybridization as Tyagi's method looks for an increase in fluorescence, thus requiring a base line for comparison. The artisan would have a reasonable expectation of success as the artisan is merely substituting the specific labels and substrates of Weiss and Gold into the method of Tyagi.

Response to Arguments

This is a new ground of rejection necessitated by amendment. The instant response provide no arguments to the instant rejection.

3. Claims 23, 25, 29 rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (US Patent 5,925, 517 Issued July 20, 1999) in view of Weiss et al (US Patent 5,990, 479 issued (Nov 23, 1999) and Gold et al (WO/1999/31275, Published June 24, 1999) as applied to claims 5, 6 and 24-25 above, and further in view of Arnold et al (WO 00/50869, published 8/31/2000).

It is noted that claim 25 requires attaching of a second label, however it does not require the detection of the label.

The teachings of Tyagi, Weiss and Gold are set forth above.

Tyagi, Weiss and Gold do not teach attaching a second label after or during hybridization.

However, Arnold teaches of method of detecting SNPs by hybridization of a second probe to a target sequence that is hybridized to a microarray (abstract). Arnold teaches the probes can be labeled with fluorescent labels (page 6). Arnold teaches this method allows for detection of SNPs in parallel (page 2).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Tyagi, Weiss and Gold by use of the sandwich SNP detection method of Arnold. The artisan would be motivated to use the SNP detection method of Arnold in conjunction with nucleic array detection method of Tyagi, Weiss and Gold because it would allow for detection of SNPs in the addition to larger nucleic acid

sequences in a single assay. Further it would have been obvious to replace the fluorescent dyes taught by Arnold with the semiconductor nanocrystals of Weiss because semiconductor nanocrystals are more stable, have a broader absorption spectrum and narrower emission spectrum. The combination of Tyagi, Weiss, Gold and Arnold would result in a method in which a first label is associated with a loop structure prior to hybridization, and detection and a second label is added before or after hybridization.

Response to Arguments

This is a new ground of rejection necessitated by amendment. The instant response provide no arguments to the instant rejection.

4. Claims 5-7, 11-14, 23-25 and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn et al (US Patent 6264825 issued July 24, 2001) in view of Weiss et al (US Patent 5,990, 479 issued (Nov 23, 1999).

Claim interpretation

The claims have been amended such that they no longer require a magnetic particle, however the claims recite open language of "comprising" and thus allow for the inclusion of additional elements and steps.

Blackburn et al teach a detector which comprises an electrode capable of detecting electron transfer (column 2, lines 14-24). A probe is immobilized on the detection electrode (column 13, lines 10-13). The "capture binding ligands" of Blackburn et al are interpreted as probes because they are capture probe nucleic acids (column 40, lines 29-40), and they allow the attachment or the target analyte to the detection electrode for the purposes of detection (column 39, lines 12-65). The probe of Blackburn et al comprises an ETM (column 66, lines 9-

44) wherein an ETM is an electron transfer moiety (abstract). Blackburn further teaches the invention may comprise an additional label at one or more positions including fluorescent dyes (column 78, lines 26-30)

Blackburn et al further teach the probe is an oligonucleotide having a hairpin stem-loop structure with the ETM moieties 135 at an end of the probe (column 66, lines 9-44 and Figure 12), wherein either the 3' or 5' terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25). Thus, Blackburn et al teach an embodiment wherein in the absence of the specific interaction of hybridization between the target and the probe, ETM moiety 135 is in a first position close to the electrode because the other end of the probe is immobilized. Upon binding to the target, the hairpin stem loop structure becomes a linear double strand, thereby disrupting the internal hybridization of the stem loop, which moves the ETM moiety further away from the electrode to a second position (Figure 12 and column 6, lines 15-22).

The first and second positions give rise to distinguishable events detectable by the electrode because detection of the binding proceeds through the use of the ETM moieties (Abstract).

While Blackburn et al also teach either the 3' or 5' terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25) so that one terminus of the probe is immobilized and the ETM moiety 135 at the other terminus, Blackburn et al do not teach the end of the probe bearing the ETM moiety moves closer to the electrode upon binding the target; i.e., the second position is closer to the electrode than the first position.

Blackburn et al teaches a method of detecting an analyte by electron transfer moiety (ETM) (see abstract). Blackburn et al further teaches the use of silicon containing moieties as labels (see column 27, line 1). Blackburn et al teaches the detection of the use of a plurality of gold electrodes (see column 2, lines 60-65). Blackburn further teaches the detection of probes prior to any experiment for use as an internal control for calibration of an experiment (see column 48, lines 4-14) (claim 7). Blackburn teaches the enzymatic incorporation of an ETM (label) during PCR (see column 60, lines 8-11). Blackburn et al further teaches the detection of the presence of ETM on the surface of the electrodes by amperommetry, voltametry, capacitance or impedance (see column 81, lines 55-67) (claim 11).

With regards to claim 12, Blackburn teaches the use of magnetic particles can be used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines 33-39). Thus Blackburn's use of magnetic particles to selectively move the ligand complex to the electrodes where it is detected results in detection based on discrimination (movement on magnetic particles) and detection by electronic means at electrode.

With regards to claim 13, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80, line 47). Electrochemiluminesence is activation of chemilumensence by a current. Thus the increase in the current results in detection of an optical signal.

With regards to claim 14, Blackburn teaches the use of magnetic particles used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines

33-39). Further, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80, line 47). Electrochemiluminesence is activation of chemilumensence by a current. Thus the increase in the current results in detection of an optical signal. Thus Blackburn teaches the detection/discrimination of a chemical reactant complex comprising the use of discriminating on magnetic signal, current values and optical. Thus Blackburn teaches detection of electrical and optical changes before and after hybridization.

Blackburn does not teach the use of a semiconductor as a label.

However, Weiss et al teaches that semiconductor nanocrystals probes are an improvement over other labels as they have a wide absorption band and a narrow emission band, while being stable (column 2, lines 3-15). Weiss teaches that semiconductor nanocrystals can label nucleic acids (column 6, lines 63-66). Weiss teaches that the nanocrystal can be linked to avidin or streptavidin which can target biotin on the probe 9column 10). Thus the use of biotin and avidin or streptavidin results in a two step process of labeling.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the semiconductor nanocrystal probes taught by Weiss in the method of Blackburn. The artisan would be motivated because to use the semiconductor nanocrystal labels of Weiss teaches the semiconductor nanocrystals are more stable, have a broader absorption spectrum and narrower emission spectrum, further Blackburn suggests fluorescent dyes can be used at any position in the probes. The artisan would have a reasonable expectation of success as the artisan is merely substituting the

fluorescent nanocrystal dyes of Weiss which have improve properties in place of the fluorescent dyes of Blackburn .

Response to Arguments

The response asserts that the previous rejection of Gold in view of Blackburn was improperly combined as it asserts the examiner does not explain why an artisan would select the components of Blackburn's invention to combine with Gold. The instant rejection was obviated those issues as the instant rejection is based on the combination of Blackburn and Weiss and is substituting nanocrystal semiconductors for the fluorescent labels of Blackburn.

The response asserts that Blackburn does not teach or suggest attaching a label to loop structured nucleic acid probe prior to hybridization and that this attachment is a key step in the claimed method. This argument has been thoroughly reviewed but is not considered persuasive as Blackburn does teach attaching of probes prior to hybridization (column 66, lines 9-44 and Figure 12) and that the molecules of the invention can contain additional labels (column 78, lines 26-30), thus making it obvious to use the semiconductor nanocrystals of Weiss.

Summary

No claims are allowed

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Juliet C Switzer/
Primary Examiner, Art Unit 1634